

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 6

REMARKS

Claims 16, 19-20, 32-39 and 157-165 were pending in the subject application. Applicants have canceled claim 39, amended claims 16, 34-38 and 161-165. Accordingly, claims 16, 19-20, 32-38 and 157-165 are pending.

Support for the amendment to claim 16 can be found in the specification inter alia on page 6, lines 12-15 and on page 78, claim 16 of the specification as originally filed.

Support for the amendment to claim 158 can be found in the specification inter alia on page 6, lines 26-34 of the specification as originally filed.

In Section 1 of the March 10, 2006 Office Action, the Examiner noted that in view of Applicants' December 3, 2004 Amendment, no outstanding ground of rejection is maintained and the Amendment is fully responsive to the Office Action as the record stood at the time. The Examiner, however, has applied new grounds of rejection and made the present Office Action non-final.

Rejection under 35 U.S.C. §112

In section 2 of the March 10, 2006 Office Action, the Examiner rejected claims 16, 19, 20 and 32-39 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner alleged that the specification, while being enabling for a pharmaceutical composition comprising a pharmaceutically acceptable carrier and terpolymers of randomly polymerized tyrosine, alanine and lysine or said pharmaceutical composition in an amount

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 7

effective to treat multiple sclerosis, does not reasonably provide enablement for the broad recitation of treating an autoimmune disease or for the diseases recited in claims 34-39 other than multiple sclerosis. The Examiner further alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner alleged that Claim 16 broadly recites a pharmaceutical composition for the treatment of autoimmune disease. The Examiner asserted that the meaning of a pharmaceutical composition is understood in the art as being a composition made for the in vivo treatment of a subject. The Examiner alleged that claim 34 broadly recites all B cell mediated autoimmune diseases; claim 35 broadly recites all T cell mediated autoimmune diseases; claim 36 broadly recites any autoimmune arthritic conditions; claim 37 broadly recites any autoimmune demyelinating disease and claim 38 broadly recites any inflammatory disease that is autoimmune. The Examiner further alleged that Claim 39 recites a number of autoimmune diseases for treatment by the claimed pharmaceutical composition.

The Examiner further alleged that while the specification is enabled for the recitation of a pharmaceutical composition comprising the recited terpolymers and a pharmaceutically acceptable carrier, the only autoimmune disease that the specification is enabled for reciting in the claims is multiple sclerosis.

The Examiner alleged that the effectiveness of treating a response to an autoantigen is dependent on several factors,

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 8

the most critical of which is whether the therapy can be used to treat an ongoing autoimmune response or whether it is only effective prophylactically, citing to Tisch, et al., Proc. Nat. Acad. Sci. (USA), 1994, 91:437-438, ("Tisch"); U1 on form PTO-892, page 437, column 2, last paragraph in particular. The Examiner alleged that typically, an autoimmune disease is diagnosed only after significant tissue damage has already occurred and that administration of an antigen after pathogenic T cells have been activated may have an exacerbating effect on the disease, rather than a tolerogenic one. The Examiner also alleged that another problem during the treatment of autoimmune diseases is determinant spreading during the course of the disease, asserting that Tisch also teaches that "the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM, and RA, in which there are responses to several autoantigens [...] and the critical inciting autoantigen(s) is not known" (page 437, third full paragraph of column 3 in particular). The Examiner alleged that the breadth of Applicants' claim is such that it recites a composition for the treatment of unrelated autoimmune diseases with a random-sequenced peptide terpolymer of a similar amino acid composition to myelin basic protein (MBP), an antigen related to the etiology of multiple sclerosis (MS) and the animal model experimental allergic encephalomyelitis (EAE). The Examiner stated that the specification demonstrates that prophylactic incubation of cells with the terpolymer inhibits T cell proliferation in response to MBP (Example 6) and inhibits a collagen-specific T cell response (Example 9). The Examiner concluded that specification does not, however, indicate that any other autoimmune diseases, could be successfully treated with the terpolymer of the invention, as in each case the examples show only prophylactic success in

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 9

inhibiting a response of a previously characterized T cell line to a single well-defined antigen and does not address the effect of an ongoing autoimmune condition where reactivity is directed to multiple antigenic epitopes. The Examiner referred to Example 10 of the instant specification and alleged that copolymer 1 inhibits activation of T cells reactive with a single antigenic epitope of the acetylcholine receptor (AChR). However, the Examiner noted, myasthenia gravis (MG) is well known by practitioners to involve reactivity to a plurality of antigenic epitopes on the AChR, not a single epitope, and that the epitopes recognized can vary greatly between MG patients.

The Examiner further alleged that while Guillain-Barre and MS are both autoimmune demyelinating diseases, the cells under attack are different and the antigenic protein is not the same.

Therefore, the Examiner asserted that, based upon the lack of guidance in the instant specification, an artisan would not be able to predict any specific autoimmune diseases that would be treatable with a pharmaceutical composition of the present invention.

Applicants' Response

Applicants initially point out that claims 16, 19, 20, 32 and 33 recite a product for which at least one use has been acknowledged to be enabled (multiple sclerosis was acknowledged to be an enabled use of the claimed pharmaceutical composition of page 3 of the March 10, 2006 Office Action). Accordingly, there appears to be no basis of record for the rejection of product claims 16, 19, 20, 32 and 33, as amended.

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 10

Applicants also note that the rejection under 35 U.S.C. §112 in the March 10, 2006 Office Action is similar to the rejection made in the January 29, 2004 Office Action. Accordingly, Applicants hereby incorporate by reference and reiterate the arguments made in Applicants' June 1, 2004 Amendment in Response to the January 29, 2004 Office Action. Applicants note that their June 1, 2004 arguments were accepted, as evident from the fact that the rejections were withdrawn in the September 13, 2004 Office Action, but were not squarely rebutted in the March 10, 2006 Office Action despite the reintroduction of a substantially similar rejection.

Notwithstanding, Applicants respectfully traverse the Examiner's rejection on the basis that the examples provided in the subject specification are reasonably predictive of, and enable, Applicants' claimed invention as explained in detail below.

It is well settled that clinical trials are not required to satisfy the enablement requirement for patentability. A claimed invention is enabled when the specification provides representative examples that correlate to the claimed invention. M.P.E.P. §2164.02 elaborates:

The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 11

disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless the examiner has evidence that it does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications)(emphasis added).

Applicants have provided in the specification several examples using recognized models of autoimmune diseases (e.g., EAE suppression, inhibition of the response of collagen specific T cells and myasthenia gravis antigenic peptide T cells) that correlate with the treatment of a number of autoimmune diseases. No evidence has been cited in the March 10, 2006 Office Action showing that the models do not correlate.¹ In addition, Applicants have also provided in the specification HLA binding data which is a working model that correlates to autoimmune diseases generally.

¹ Tisch et al., the only reference cited in the March 10, 2006 Office Action, does not provide evidence of lack of correlation. On the contrary, Tisch et al. endorse the predictive value of "models of autoimmunity." See, Tisch et al, p. 428, column 1, middle paragraph.

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 12

Specific Autoimmune Diseases and Respective Model(s)

The subject application provides a number of accepted models of specific autoimmune diseases. Treatment of such specific autoimmune diseases must be found to be enabled by the models provided, especially in view of the lack of any evidence to the contrary. Accordingly, treatment of the following specific autoimmune diseases must be found to be enabled:

1) Multiple Sclerosis

The correlation between the EAE model and multiple sclerosis is well established and has been accepted by the Examiner. The subject specification shows that mixtures of polypeptides, as claimed, suppress EAE (Example 3, pages 30-34 of the subject application).

In addition, the subject specification shows that mixtures of polypeptides, as claimed, inhibit MBP-induced T cell proliferation (Example 6, pages 43-46 of the subject application), stimulate COP-1 specific T cells (Example 7, pages 46-48 of the subject application), and cross react with anti-COP-1 antibodies (Example 8, pages 48-51 of the subject application), thus implicating autoimmune diseases beyond multiple sclerosis.

2) Rheumatoid Arthritis

Type II collagen is known to induce arthritis in animal models. As such, molecules that compete with collagen in binding to HLA-DR molecules, thus inhibiting collagen-specific T cells response, have been proposed by skilled artisans as compounds for treating rheumatoid arthritis (Fridkis-Hareli, PNAS, 1998, Vol. 95, pp 12528-31).

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 13

As acknowledged by the Examiner on page 3 of the March 10, 2006 Office Action, Applicants have shown that the claimed terpolymers inhibit collagen-specific T-cell response (page 15, lines 21-29, page 17, line 28 to page 18, line 1 and page 52, Example 9 of the subject application). Inhibition of collagen-specific T-cell response correlates to a treatment of rheumatoid arthritis (Fridkis-Hareli, PNAS, 1998, Vol. 95, pp 12528-31).

As further support for their claim to treatment of rheumatoid arthritis, Applicants have shown that the terpolymers of the subject application bind to HLA-DR1 and HLA-DR4 (Example 5, pages 37-43 of the subject application). Rheumatoid arthritis has also been correlated with human leukocyte antigens HLA-DR1 and HLA-DR4 (Fugger, et al. Arthritis Research 2000, 2: 208-211).

3) *Myasthenia Gravis*

Applicants have shown that copolymer 1 inhibits T cells responsive to a myasthenia gravis antigenic peptide (Example 10, pages 56-58 of the subject application). The correlation of acetylcholine receptor as a model for myasthenia gravis is well accepted in the art (Boyton, et al., Clin. Exp. Immunol., 2002, 127: 4-11).

As further support for their claim to treatment of myasthenia gravis, Applicants have shown that the terpolymers of the subject application bind to human leukocyte antigens ("HLA") (Example 5, pages 37-43 of the subject application). Myasthenia gravis has also been correlated with human leukocyte antigens (Giraud, et al., Neurology, 2001 57(9): 1555-60).

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 14

4) *Other Autoimmune Diseases Correlated to Human Leukocyte Antigens (HLA)*

Indeed, a number of autoimmune diseases have been correlated with human leukocyte antigens by practitioners in the art. The following list of claimed diseases is merely representative:

Disease	HLA	Reference
autoimmune thyroiditis	HLA-DR3	Wan, et al., Human Immunology 2002, Apr. 63(4):301-10
autoimmune uveoretinitis	HLA-DR4	Giuseppina, et al., The Journal of Clinical Investigation, April 2003, Vol. 111, No. 8, 1171-80
colitis	HLA-DR4	Kobayashi, et al., Clin Exp Immunol. 1990 Jun;80(3):400-3
diabetes mellitus	HLA-DR4	http://ntri.tamuk.edu/immunology/autoimmunity.html
Graves disease	HLA-DR4	Sridama, et al., Arch Intern Med. 1987;147:229-231
Hashimoto's disease	HLA-DR4	Lymberi, et al., Arch Hellen Med, 16(4), July-August 1999, 337-351
psoriasis,	HLA-DR4	Fatma, et al., Swiss Med Wkly, 2003, 133: 541-543
pemphigus vulgaris	HLA-DR4	Lombardi, et al., J Invest Dermatol. 1999 Jul;113(1):107-10
systemic lupus erythematosus	HLA-DR4	Batchelor, et al. Lancet 1980 1(8178):1107-9

Applicants have shown that the claimed mixtures of terpolymers bind to HLA-DR 1, 2, and 4 (Example 5, pages 37-43 of the subject application). Therefore, particularly in the absence of any evidence of record to contradict each of the above references showing the correlation to a respective disease, Applicants' claims to treatment of these diseases must be deemed to be enabled.

Autoimmune Disease Genus

In addition, the numerous models provided in the subject specification for the diseases discussed above constitute numerous working examples for treatment of autoimmune diseases

Applicants : Aharoni, et al.
Serial No. : 09/768,872
Filed : January 23, 2001
Page 15

generally. Applicants point out that, for example, the human leukocyte antigens binding models are well accepted to be key elements of the immune response and generally associated with autoimmune diseases as a class (Mallios, Bioinformatics, 1999, Vol. 15, No. 6, 432-439).

Accordingly, Applicants' numerous working examples not only provide enablement for the specific autoimmune diseases discussed above, but additionally serve as evidence of enablement of a representative number of species of the autoimmune disease genus (M.P.E.P. §2164.02).

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.